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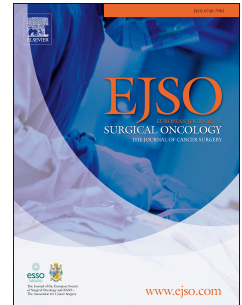
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# Accepted Manuscript

Image guided therapy and the importance of local tumour control

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Contemporary cancer care is multidisciplinary and should provide evidence based and protocol driven advice to patients, aiming for cure or relief of symptoms at as little personal cost to patients as possible, while minimising the financial burden to the system. The achievement of locoregional cure may involve combinations of systemic therapy, surgery and radiotherapy, aiming for maximal organ preservation and function.<sup>1,2</sup>

The use of modern imaging has revolutionised the care of people affected by cancer. It contributes to the staging of their disease, facilitates the planning of appropriate local and systemic treatment and enables monitoring of the outcomes of the therapeutic interventions chosen. Imaging underpins sophisticated radiation therapy and is integral to interventional radiology.

In solid cancers, systemic treatment can be used to reduce the likelihood of systemic relapse, and increase the rate of locoregional cure following surgery and radiotherapy. Chemotherapy accounts for a surprisingly small proportion (less than 3%) of long-term cures in solid cancers.<sup>3</sup> Nevertheless, despite the critical importance of locoregional cancer cure, systemic therapy has a much higher community profile than local cancer treatments and accounts for a greater proportion of health care costs and research funding than surgery, radiation treatment and interventional ablative techniques.

Patients, in whom local cure is not achieved face a significantly greater risk of developing metastatic disease. This has been demonstrated in most cancer subtypes and patient populations.<sup>4,5</sup> A greater appreciation of the importance of local therapies in patients with no appreciable or minimal metastatic disease, and a new focus on their critical role in the care pathway, is very timely.

Imaging is of particular importance when considering local tumour treatment. All local therapies, including surgery, radiotherapy and ablative interventional techniques are dependent on and heavily influenced by the accurate demonstration of the location and size of the tumour to be targeted, as well as its relation to adjacent structures. When planning surgical procedures, the demonstration of loco-regional involvement aids careful preoperative, and sometimes intraoperative, planning and treatment. The use of imaging to guide therapy, as distinct from diagnosis, can have a profound impact on the methods of treatment of localized malignant disease and this is particularly evident in the fields of radiation oncology and interventional oncology. Advanced imaging, along with computerised planning, enables the delivery of highly focussed and sculpted radiation dose clouds and lies at the core of modern radiotherapy. Interventional radiological techniques are guided by images obtained at the time of treatment, which enable the accurate placement of instruments in the most effective position. A variety of interventional modalities, including selective internal radiation treatment, radiofrequency and microwave ablation, cryotherapy, and newer techniques such as irreversible electroporation, can be used to treat cancer.

Although surgery will remain the cornerstone of managing larger non-metastatic cancer, the detection of solid tumours at a very early stage raises the question of whether it should remain the first line method of treatment for small malignant tumours. The same oncological principles that have made possible the performance of less radical surgery in breast cancer with excellent oncological outcomes should be applied to new techniques of imaging-guided therapy, such as Stereotactic Ablative Radiation Therapy (SABR), thermal ablation and cryotherapy. However, this has to be done on the basis of the best available evidence at every stage of exploration of such new developments.

There are great difficulties in performing randomised studies comparing interventions in different procedural disciplines. These are multifactorial and include patient selection and their willingness to be randomised, as well as controlling for the skill of the individual operator and assurance of the quality of the care delivered. However, there is now substantial evidence that in some solid tumours imaging guided techniques may be able to produce similar oncological results to surgery.

In hepatocellular carcinoma liver transplantation achieves the best oncological outcomes but its use is restricted by the shortage of donor organs. Surgical resection was accepted as a treatment of choice before the era of transplantation but is not a realistic option in many patients because of poor hepatic reserve, multifocal disease or inability to obtain an optimal tumour free margin. Therefore, for the majority of patients with hepatocellular carcinoma, loco-regional therapy with ablation is the only alternative treatment option.

In the case of small renal tumours partial or radical nephrectomy is often not carried out because the risks of surgery are thought to outweigh the dangers of the tumour metastasizing. However, evidence is now emerging that the risks of small renal tumours have been underestimated, probably because patients referred to urologists are less likely to have metastases, thus introducing a bias in studies performed by urological centres. An analysis of a Swedish national registry has shown that small renal cell carcinomas can have significant potential for aggressive growth and the development of metastases.<sup>6</sup> A recent meta-analysis suggested that the oncological outcomes of nephron-sparing surgery and thermal ablation are similar.<sup>7</sup> In the light of such evidence it is reasonable to reassess the indications for intervention in such patients: if a malignant tumour can be eliminated with similar oncological outcomes to surgery but with fewer major complications, less discomfort to the patient and lower costs to the patient and the system, there may be a good case for image-guided ablative treatment of patients whose tumours would otherwise have been observed rather than resected.

Radiation oncology and interventional oncology have much in common. Both disciplines rely on exquisite imaging, and both focus on local tumour treatment. SABR delivers high dose radiation treatment in one or a small number of treatments and is the treatment of first choice in medically unfit patients with small malignant pulmonary tumours. We can foresee the time when it will replace surgical resection for small lung cancers. A number of well designed trials randomising operable patients with small lung cancers to surgery or SABR have closed early due to poor accrual, demonstrating the difficulty of randomisation in these treatments.

Thermal ablation and cryotherapy may also achieve excellent results in such patients. The mechanisms of action of radiotherapy techniques differ from those employed in interventional oncology, offering the potential of combining thermal ablation or cryotherapy with radiotherapy, for the purpose of reducing the risk of local recurrence and improving outcomes.

When cure is no longer the goal, local treatment can be very helpful to patients with complex or symptomatic metastases either on its own or in addition to palliative systemic therapy. Interventional oncologists can relieve obstruction and ablate troublesome metastases. Local

palliative radiation therapy can be of great value in relieving local symptoms and these treatments, used wisely, may improve significantly the quality of life of patients.

The concept of oligometastatic or low volume metastatic disease, particularly in patients with long disease free intervals, raises some important issues in relation to local tumour treatment. The existence of an apparent oligometastatic state is distinctly uncommon in clinical practice; it is controversial and is the subject of intense current debate. Nonetheless, for some patients who either have an apparent single metastasis or a dominant metastasis on a background of other minimal disease, local control ensuring freedom from symptoms or local tumour complications for the duration of their life is of great value. In some patients this may have the potential to prolong survival.

The evidence base underpinning radiation therapy is vast and of high quality. For the newer ablative radiotherapy techniques, the evidence is growing rapidly. Randomisation of patients to standard surgical intervention versus either interventional oncology techniques or ablative radiotherapy is challenging. However, where there is equipoise, or an apparent advantage in interventional treatment, evidence needs to be amassed to support its use. The hierarchy of evidence that is considered when making decisions regarding research funding, clinical practice guidelines and care delivery requires reassessment. Phase 3 randomised trials have dominated thinking in oncology, particularly in relation to systemic treatment. However, where technology and techniques are evolving rapidly, other forms of high quality evidence, such as comparative effectiveness studies using sophisticated registries, are likely to be particularly relevant.<sup>8</sup> Such registries should also incorporate patient reported outcomes measures and assessments of overall economic impact. This may be the only way of collecting relevant high quality data, if patients are not to be denied the benefits of emerging minimally invasive methods of treatment.

Radiation oncology is a cornerstone of integrated modern cancer care. Interventional oncology has the opportunity to make a major contribution to modern oncology, and to become its fourth pillar, alongside surgery, radiation therapy and systemic treatment. All oncologists should consider how to nurture and support this discipline, and how best to integrate it into multidisciplinary care.

The fact that interventional oncology is not yet a mature oncological discipline is a significant impediment to the appropriate development of this specialty. Interventional oncologists need to be welcomed into multidisciplinary teams and receive formal oncology training if they are to communicate effectively and collaborate with surgeons, radiation oncologists, medical oncologists and patients. They must also practise within a quality framework while constantly collecting the evidence to support their treatment methods.<sup>9</sup> Fortunately, rapid progress is being made in relation to the achievement of these goals. It is likely that in the next few years, advances in molecular and functional imaging will combine with the development of more sophisticated methods of image-guided therapy to further revolutionise the clinical management of patients with malignant tumours in solid organs.

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